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SPARING EFFECT OF CHRONIC HIGH-ALTITUDE EXPOSURE ON MUSCLE GLYC--ETC(U)
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Sparing Effect of Chronic High-Altitude Exposure on Muscle Glycogen Utilization During Exercise

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Running Head: Glycogen Sparing at High Altitude

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ABSTRACT

Substrate utilization during heavy (~ 85% $\dot{V}O_2$ max) bicycle exercise was examined in eight low-altitude residents at sea level (SL) and after acute (2 hours) and chronic (18 days) exposure to 4,300 m (HA). Mean $\dot{V}O_2$ max was ~ 27% lower with acute HA than at SL and did not change significantly with continued HA exposure. Biopsies from the vastus lateralis muscle and venous blood samples were obtained before and after 30 min of exercise, while determinations of the respiratory exchange ratio (R) were made at 10 min intervals during each of the submaximal bouts. Resting serum levels of free fatty acids, unchanged with exercise, were 2X and 3X higher than SL with acute and chronic HA, respectively. Exercise did not alter resting serum glycerol levels at SL or during acute HA, but caused an 11-fold increase during chronic HA. Mean blood lactate concentrations were similar following exercise at SL and acute HA but were 87% lower after chronic HA. During exercise at SL and acute HA, the rate of muscle glycogen utilization and R were similar but were 41% and 15% lower, respectively, with chronic HA. These data suggest that after chronic high-altitude exposure, increased mobilization and use of free fatty acids during exercise resulted in sparing of muscle glycogen.

Key Words: fat metabolism; blood lactate; blood free fatty acids; blood glycerol; hypobaric hypoxia; adaptation to high altitude

INTRODUCTION

In two previously reported studies, endurance time at a given submaximal exercise intensity was observed to increase during short-term residence at high altitude. Maher et al. (20) reported that endurance time of subjects residing for twelve days at 4,300 m was increased by 45% (day 2 vs. day 12). In that study, subjects cycled at intensities equal to 75% of their maximal aerobic capacity ($\dot{V}O_2$ max). Horstman et al. (15) observed a 59% increase in running time to exhaustion (85% of $\dot{V}O_2$ max) between the first and sixteenth day of residence at 4,300 m. The investigators differed in their explanation for the increased endurance time. Maher et al. (20) ascribed the increase to a decreased anaerobic demand and rate of glycolysis during exercise. This conclusion was based on the finding that substantially less blood lactate accumulated during exercise on the twelfth day at altitude as compared to the second day. Horstman et al. (15) attributed the greater time to exhaustion to a concomitant increase in $\dot{V}O_2$ max on the fifteenth day at 4,300 m relative to the first day. Since the absolute exercise intensity was the same for both of Horstman's endurance tests, he concluded that the subjects were exercising at a lower relative exercise intensity during the latter test than during the first test.

Either of the aforementioned adaptations could account for an increased endurance time. Gleser and Vogel (11) described the relat nship between an individual's endurance time at a given exercise intensity and his $\dot{V}O_2$ max by the equation:

$$\log (t) = a \cdot (\text{load}/\dot{V}O_2 \text{ max}) + b$$

where t = endurance time, load = exercise intensity, and a and b are constants related, respectively, to the rate and quantity of anaerobic metabolism. Gleser and Vogel (11) observed that a 7% increase in $\dot{V}O_2$ max was accompanied by a 100% increase in endurance time. This equation shows also that a change in

$\dot{V}O_2$ max is not necessary for increased endurance; alterations in energy metabolism alone could result in enhanced endurance. The relationship between endurance exercise and muscle glycogen stores has been reviewed by Hultman (16) who found that subjects with higher initial muscle glycogen levels had longer endurance times and muscle glycogen levels were reduced virtually to zero in subjects who cycled (intensities >70% $\dot{V}O_2$ max) to complete exhaustion. Thus, any adaptation which resulted in a sparing of muscle glycogen during exercise could result in longer endurance times. The purpose of this study was to determine the effect of chronic high-altitude exposure on $\dot{V}O_2$ max and substrate utilization during submaximal exercise.

METHODS

After being fully informed as to the nature and requirements of the study, eight healthy male soldiers gave their consent to participate in the study as subjects. All were SL natives and none had sojourned at HA for 10 months before the study. Prior to the study, the men had participated in the usual Army physical training; however, none were highly trained. The subjects were asked to maintain their physical activity at their usual level and not begin any new training program. The subjects were allowed to eat and drink ad libitum during the study. The physical characteristics of the subjects (mean $\pm$ SE) were: age, 23.3 $\pm$ 1.3 yr; height, 175.6 $\pm$ 2.2 cm; and weight, 75.5 $\pm$ 2.5 kg.

The $\dot{V}O_2$ max of the subjects was determined on the first day of the study and every seventh day thereafter throughout the study. The first four determinations were at SL (Natick, MA: 50 m). The fifth was performed during an acute (< 2 hours) exposure to a simulated altitude of 4,300 m (hypobaric chamber pressure: 445 Torr). The subjects were transported via commercial aircraft and automobile to 4,300 m (Pikes Peak, CO) on the thirty-fifth day of the study and

$\dot{V}O_2$ max was determined on the first, eighth, and fifteenth day of continuous residence. The final $\dot{V}O_2$ max determination was completed approximately 48 hours after descent to SL. A discontinuous cycling test was used for the determination of $\dot{V}O_2$ max and the criterion for $\dot{V}O_2$ max was that $\dot{V}O_2$ increase by less than 150 ml • min^{-1} with an increase in exercise intensity of 30 W (18).

Substrate utilization during submaximal exercise was examined on three occasions: at SL, and during acute (< 2 hours) and chronic (18th day) HA exposure. For each test, subjects cycled continuously for 30 min at an intensity requiring 85% of the $\dot{V}O_2$ max determined four days previously under the same environmental conditions. Samples of the vastus lateralis muscle and venous blood were collected before, and immediately after the completion of the exercise. Respiratory exchange was measured at the fifth, fifteenth, and twenty-fifth min of exercise. If it was determined that $\dot{V}O_2$ at the fifth min was more than 5% above or below 85% of maximum, the absolute exercise intensity was raised or lowered as required. After the fifth min, however, no further adjustment in exercise intensity was allowed.

All exercise was performed on a mechanically-braked Monark cycle ergometer calibrated by hanging known weights from the pendulum. The subjects pedalled at a frequency of 60 rpm and were paced by an electronic metronome. To ensure that exercise intensity was accurately recorded, an observer counted the pedal revolutions during all respiratory exchange measurements. Respiratory exchange was determined from timed collections of the air expired by the subjects through a Collins triple-J valve connected to Douglas bags. Mixed expired O_2 and CO_2 were measured with an Applied Electrochemistry S-3A fuel cell and a Beckman LB-2 infrared analyzer, respectively. Expired gas volumes were measured using a Tissot spirometer. From these measurements, minute ventilation ($\dot{V}_E$) corrected to BTPS, $\dot{V}O_2$ and $\dot{V}CO_2$ corrected to STPD, and the respiratory exchange ratio (R) were calculated.

Muscle samples were obtained using the biopsy technique of Bergstrom (2). Specimens were quickly freed of all connective tissue, divided into several pieces and then frozen in liquid nitrogen. Samples obtained at SL and during the acute HA experiments were stored in liquid nitrogen. Samples obtained at Pikes Peak were packed in dry ice (following freezing in liquid nitrogen) for shipment to Natick and, upon arrival (approximately 30 hours after biopsy), were stored in liquid nitrogen. Two or three pieces of each sample were subsequently analyzed for glycogen (22) and the values were averaged to represent the muscle glycogen content of the sample.

Venous blood was obtained by puncture of a forearm vein. The blood was allowed to clot and the serum was then divided into three samples. Two samples were frozen and stored for subsequent analysis of free fatty acids (FFA) (8) and glycerol (30) concentrations. The third sample was frozen until lactate concentration was determined (no more than 72 hours after venipuncture) using an enzymatic kit (Sigma Chemical Co., St. Louis, MO).

Standard statistical procedures were used for data analysis. A three-way (subject X condition X time exercised) analysis of variance (ANOVA) was used to compare physiological and biochemical parameters. When a statistically significant F-ratio was calculated. differences between means were tested for statistical significance using Tukey's critical difference test. The level of significance was set at $p < 0.05$.

RESULTS

Maximal exercise.

The third and fourth determinations of $\dot{V}O_2$ max at SL were not significantly different. Data from the fourth determination has, therefore, been used to represent maximal responses at SL. Physiological responses during maximal

exercise at SL and during acute and chronic HA exposure are shown in Table 1. The $\dot{V}_E$ max at HA and at SL did not differ significantly. Maximal HR at HA was not different from SL until the fifteenth day at 4,300 m when it averaged 23 $b \cdot min^{-1}$ lower. On the eighth and fifteenth day at 4,300 m, R max was significantly lower than at SL and this reduction persisted after return to SL. Mean $\dot{V}O_2$ max (Fig.1) during acute HA exposure was 27% lower than at SL and no further significant change in $\dot{V}O_2$ max was seen with continued HA exposure; upon return to SL, $\dot{V}O_2$ was not significantly different from the previous SL value.

TABLE 1 ABOUT HERE

FIGURE 1 ABOUT HERE

Submaximal exercise.

Oxygen consumption and exercise intensity. During the 30-min submaximal exercise bout at SL, mean absolute exercise intensity (189 W) and mean $\dot{V}O_2$ ($2.90 \ell \cdot min^{-1}$) were significantly higher than during either acute HA (140 W, $1.99 \ell \cdot min^{-1}$) or chronic HA (135 W, $2.08 \ell \cdot min^{-1}$) which were not significantly different. Relative exercise intensity averaged 86% of $\dot{V}O_2$ max at SL, 80% of $\dot{V}O_2$ max during acute HA exposure, and 85% during chronic HA exposure; these values were not significantly different. Both $\dot{V}O_2$ and relative exercise intensity increased significantly between the fifth and fifteenth min with no further change by the twenty-fifth min.

Respiratory exchange. There was no significant difference between mean R (Fig. 2) during exercise at SL (1.12) or acute HA (1.11). During the chronic HA exercise, however, R was significantly lower (0.95). At SL and acute HA, there was a significant decrease in R between the fifth and fifteenth min of exercise and no further changes occurred after twenty-five min. During chronic HA exercise, there were no significant differences in R at any time. The $\dot{V}_E$ during exercise averaged $123.6 \ell \cdot min^{-1}$ at SL, $122.5 \ell \cdot min^{-1}$ at acute HA, and $133.2 \ell \cdot min^{-1}$ at chronic HA; differences between means were not significant.

FIGURE 2 ABOUT HERE

Ventilatory equivalent ($\dot{V}_E/\dot{V}O_2$) was significantly higher during exercise at HA (acute and chronic) than at SL (Fig. 3). Both $\dot{V}_E$ and $\dot{V}_E/\dot{V}O_2$ were significantly higher after 15 min of exercise than after five min but no further change occurred.

FIGURE 3 ABOUT HERE

Serum lactate, glycerol and FFA. Resting serum FFA (Fig. 4A) concentrations did not change during the three exercise bouts but were significantly higher than SL with acute (2X) and chronic (3X) HA. Serum glycerol concentrations (Fig. 4B) were not significantly changed during exercise at SL or acute HA but were substantially increased during exercise on the 18th day at HA. There were no significant differences in resting blood glycerol concentrations at SL or chronic HA but acute HA was associated with a significant increase. Resting blood lactate concentration (Fig. 4C) after chronic HA exposure was lower than at SL or during acute HA exposure when there was no difference. The increase in serum lactate concentration during exercise at SL and acute HA was not significantly different. After chronic HA exposure, however, blood lactate accumulation was significantly reduced.

Glycogen utilization. Muscle glycogen concentrations before and after each submaximal exercise bout are shown in Fig. 4D. Resting levels of muscle glycogen were not different from SL during acute HA but were significantly lower with chronic HA. Post-exercise muscle glycogen levels at SL and chronic HA did not differ significantly but were significantly higher during acute HA. The change (resting minus post-exercise) in muscle glycogen (expressed as glucose) concentration during exercise averaged 48.4 mMoles $\cdot$ kg^{-1} at chronic HA, the latter being 42% less than the SL value, a significant difference in muscle glycogen utilization during chronic HA exercise.

FIGURE 4 ABOUT HERE

DISCUSSION

The reduction in maximal aerobic capacity during acute high-altitude exposure persisted with no significant improvement with continued residence at altitude. Although this finding is in contrast to the recent report of Horstman et al. (15), it is in general agreement with the work of others (4,10,27). In the present study, there were no training or detraining effects during the altitude sojourn; $\dot{V}O_2$ max upon return to sea level was not different from that measured before the sojourn.

Pre-exercise muscle glycogen concentration on the eighteenth day of HA residence was significantly less than at SL. The reduced resting glycogen concentration may have resulted from an incomplete repletion following the maximal exercise performed earlier in the week. The commonly observed anorexia at high altitude would tend to slow restoration of glycogen stores. Post-exercise glycogen concentrations did not differ. The question is raised as to whether the reduction in the amount of glycogen depletion with chronic altitude exposure is a reflection of the reduced resting levels or represents a true sparing of muscle glycogen. It has been shown that the utilization of muscle glycogen can continue until the concentration has fallen nearly to zero (16). In addition, the amount of muscle glycogen utilized has been shown to be independent of the pre-exercise concentration for ranges including those observed in the present study (5). In none of the three exercise bouts was the post-exercise glycogen concentration less than 50% of the initial concentration. It is concluded, therefore, that the reduction in the amount of glycogen depletion represents a true sparing effect of HA exposure.

Sparing of muscle glycogen during exercise has previously been demonstrated to result from increased physical training (14), caffeine ingestion prior to exercise (9) and elevation of blood FFA levels by heparin administration (6). In

all of these studies, the sparing effect on muscle glycogen was related to enhanced mobilization and utilization of free fatty acids during exercise. Data obtained in the present investigation suggest that chronic altitude exposure also results in increased reliance on fats as an energy source during exercise. There was a large increase in serum glycerol concentration during exercise on the 18th day of altitude residence which was not observed during exercise at SL or during acute altitude exposure. FFA are released in approximately a 3:1 molar ratio with glycerol during lipolysis. The large increase in serum glycerol concentration during exercise was not associated with a three-fold greater increase in FFA concentration; in fact, there was no change in FFA concentration. Either lipolysis was enhanced, and the increased mobilization of FFA balanced by increased uptake and oxidation by the muscle, or glyercol removal was reduced due to a reduction in hepatic blood flow. Hepatic blood flow in man has been shown to be reduced during exercise while the rate of glycerol uptake by the liver was increased (28,29). The increased glycerol uptake was due to greatly increased arterial glycerol concentration during exercise with fractional extraction maintained at or near resting level (28). Any additional effect of hypoxia on hepatic uptake of glycerol is likely to favor increased rather than decreased removal since, at least during rest, hepatic blood flow is increased at high altitude (24).

Chronic altitude exposure was associated with a reduced respiratory exchange ratio during exercise, as compared to sea level or acute exposure which further supports the conclusion that utilization of FFA was enhanced. Although R values as high as observed in this study may reflect hyperventilation, the $\dot{V}O_2$ and $\dot{V}_E/\dot{V}O_2$ were not different during acute or chronic altitude. The reduction in R does not reflect less hyperventilation. In animals, the rate of FFA oxidation by muscle has been shown to be proportional to the concentration of FFA to

which it is exposed (23). Increased utilization of plasma FFA has been shown to result in decreased utilization of muscle glycogen in both rats (13) and man (6). Finally, increased lipolysis and FFA mobilization have been reported to occur in man during hypoxic exposure (17,19).

Increased sympathetic nervous activity is a strong stimulus for lipolysis in adipose tissue (12,26). It has been demonstrated that sympathetic nervous activity is increased at high altitude (21) thus accounting for the increased mobilization of FFA during exercise on the eighteenth day at Pikes Peak. There was, however, no indication that fat metabolism was increased during exercise under conditions of acute hypoxia. At least two explanations are possible. Despite the rapid increase in sympathetic activity at high altitude (21), concentration of circulating norepinephrine is not significantly increased until ~ 36 hours of hypoxic exposure (7). Rosell (25) has shown that while stimulation of sympathetic fibers innervating subcutaneous adipose tissue of the dog produced increased lipolysis, there was also concomitant vasoconstriction and reduced blood flow to the region which restricted FFA release into the circulation. When the concentration of circulating norepinephrine was increased, however, there was a vasodilation of the vascular bed of the adipose tissue and increased release of glycerol (and therefore, presumably FFA) into the circulation (1). On the other hand, high concentrations of arterial lactate have been shown to inhibit lipolysis and FFA mobilization (3). During the acute altitude exposure, exercise resulted in large increases in lactate which were not observed with exercise on the 18th day at Pikes Peak.

In summary, the results of this study indicate that after chronic altitude exposure, there is increased mobilization and utilization of free fatty acids during exercise with associated sparing of muscle glycogen. Additional studies to determine whether this adaptation persists upon descent to sea level appear warranted.

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FIGURE LEGENDS

Figure 1. Changes in maximal oxygen uptake ($\dot{V}O_2$ max) (mean $\pm$ SE) after two hours (2H), one day (1D), eight days (8D) and fifteen days (15D) at 4,300 m, and upon descent to sea level.

Figure 2. Respiratory exchange ratio (R) during submaximal exercise at sea level (SL) and during acute and chronic (day 18) high-altitude exposure (AHA, CHA, respectively).

Figure 3. Ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_2$) during submaximal exercise at sea level (SL), and during acute and chronic (day 18) high-altitude exposure (AHA and CHA respectively).

Figure 4. Changes in concentration (mean $\pm$ SE) of serum lactate, free fatty acid (FFA), glycerol and muscle glycogen, with submaximal exercise at sea level, during acute high-altitude exposure, and on the eighteenth day at altitude.

TABLE 1. Cardiovascular and respiratory responses during maximal exercise

Response	Sea Level Control	Acute High Altitude, 4300 m	Pikes Peak, 4300 m			Sea Level Post-Sojourn
			Day 1	Day 8	Day 15	
$\dot{V}O_2$ max, ($\ell \cdot min^{-1}$, STPD)	3.39 ± 0.11	2.48 ± 0.10*	2.40 ± 0.08*	2.40 ± 0.07*	2.44 ± 0.09*	3.46 ± 0.11
$\dot{V}_E$ max, ($\ell \cdot min^{-1}$, BTPS)	159.9 ± 5.8	164.5 ± 10.5	159.6 ± 5.8	176.4 ± 7.8	176.6 ± 8.0	163.3 ± 4.1
HR_{max} ($b \cdot min^{-1}$)	182 ± 3	166 ± 6	171 ± 4	169 ± 6	159 ± 7*	181 ± 2
R_{max}	1.26 ± 0.02	1.34 ± 0.04	1.24 ± 0.03	1.12 ± 0.04*	1.11 ± 0.04*	1.11 ± 0.04*

Values presented are Mean ± SE (n = 8)

* Significantly different from Sea Level Control

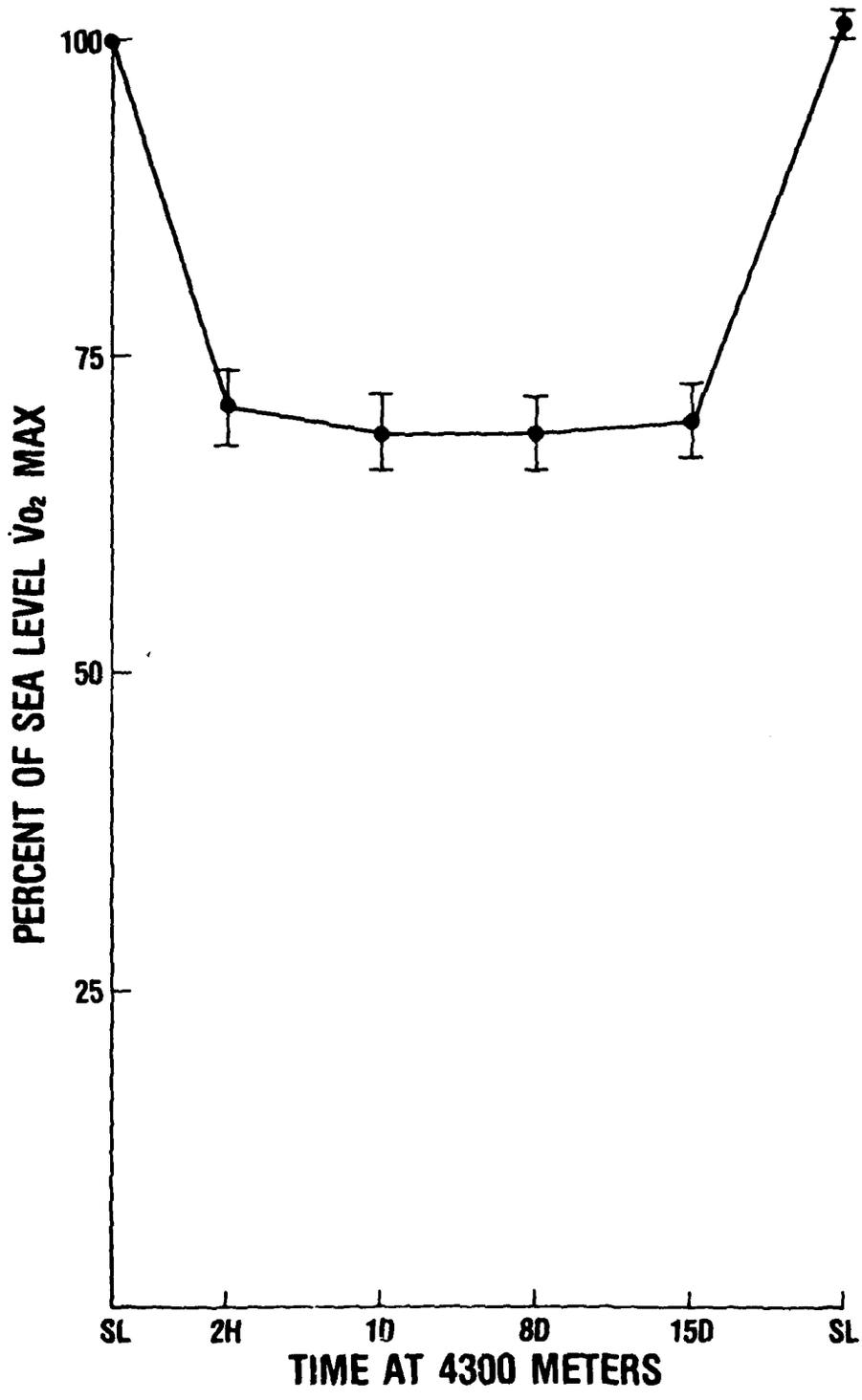
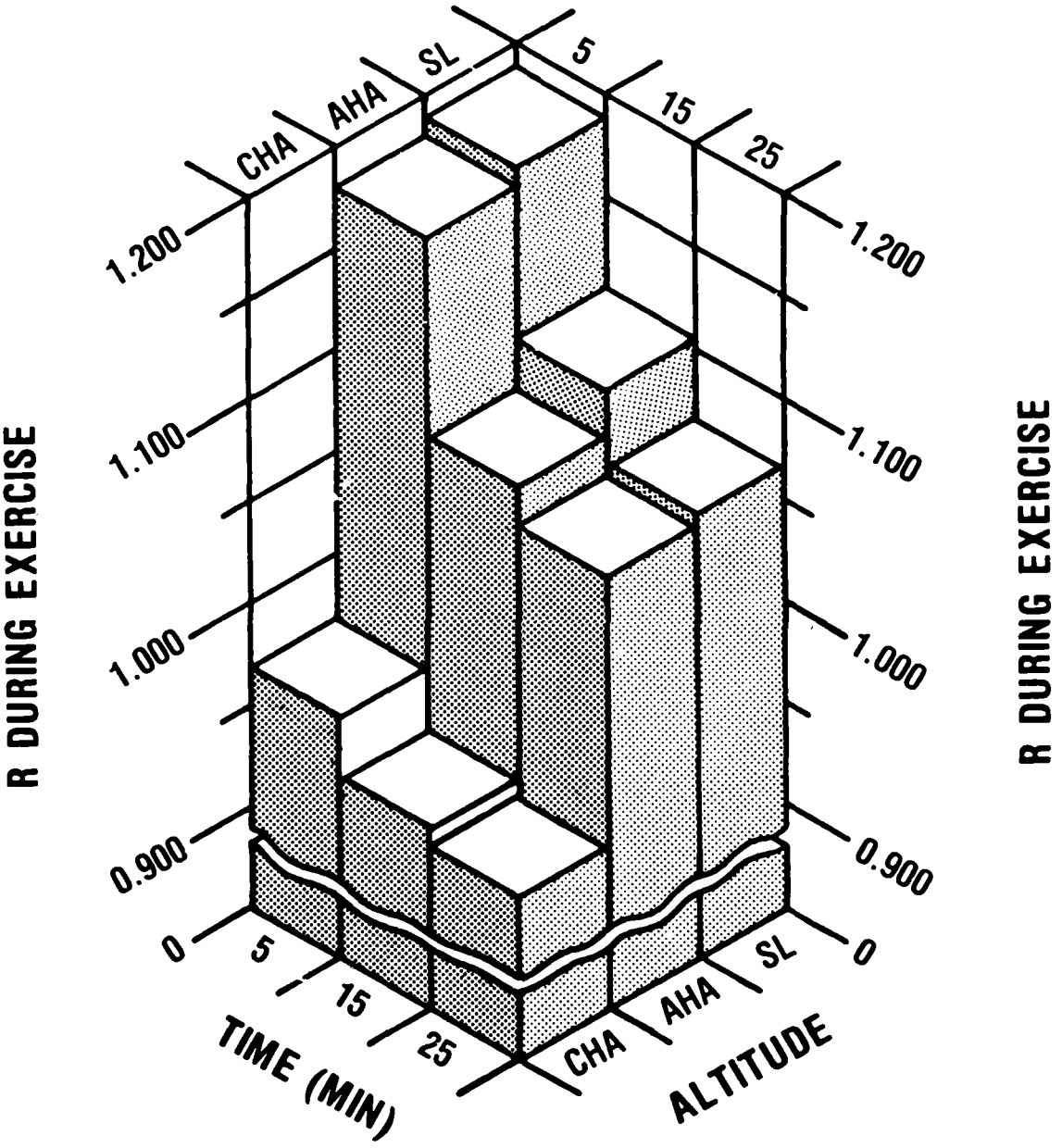

100
75
50
25
PERCENT OF SEA LEVEL $\dot{V}O_2$ MAX
SL
2H
1D
8D
15D
SL
TIME AT 4300 METERS

Fig. 1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1.200
1.100
1.000
0.900
0
5
15
25
TIME (MIN)
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AHA
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Fig. 2

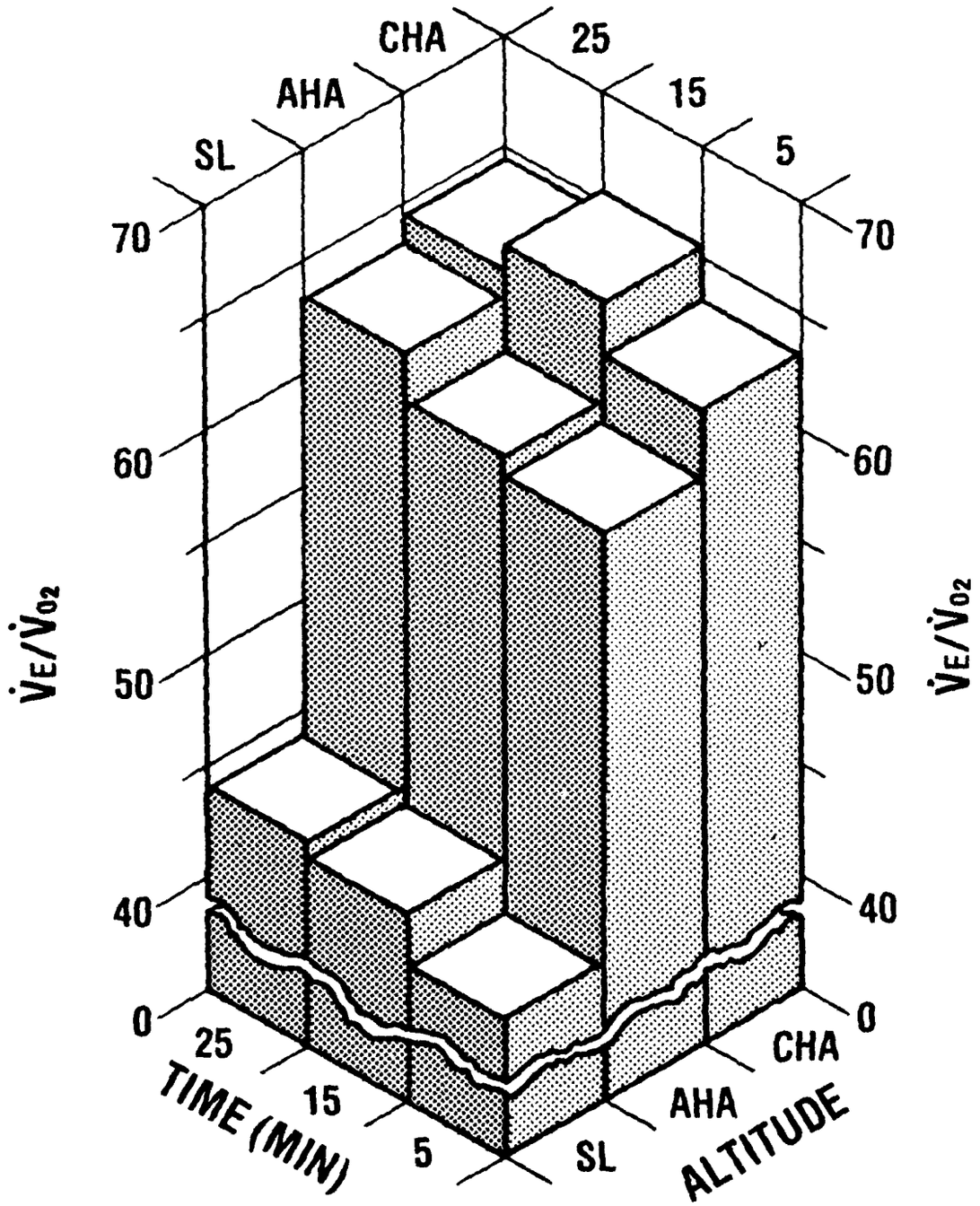
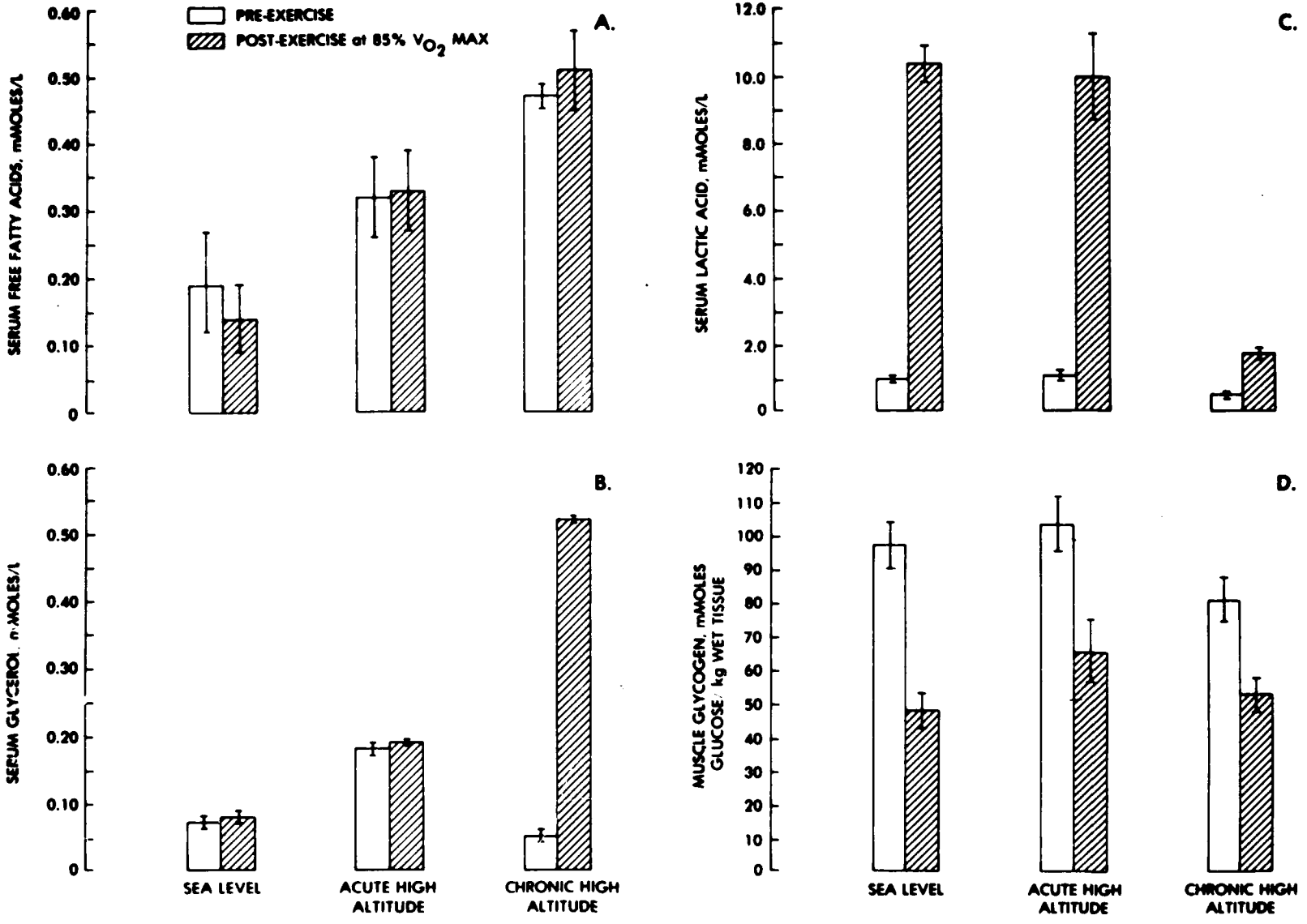


Fig. 3

Fig. 4


PRE-EXERCISE
POST-EXERCISE at 85% V_{O_2} MAX
A.
B.
C.
D.
SERUM FREE FATTY ACIDS, mMOLES/L
SERUM GLYCEROL, mMOLES/L
SERUM LACTIC ACID, mMOLES/L
MUSCLE GLYCOGEN, mMOLES GLUCOSE/ kg WET TISSUE
0.60
0.50
0.40
0.30
0.20
0.10
0
12.0
10.0
8.0
6.0
4.0
2.0
120
110
100
90
80
70
60
50
40
30
20
10
SEA LEVEL
ACUTE HIGH ALTITUDE
CHRONIC HIGH ALTITUDE

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17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

N/A

18. SUPPLEMENTARY NOTES

N/A

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

fat metabolism; blood lactate; blood free fatty acids; blood glycerol; hypobaric hypoxia; adaptation to high altitude

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Substrate utilization during heave (~ 85% $\dot{V}O_2$ max) bicycle exercise was examined in eight low-altitude residents at sea level (SL) and after acute (2 hours) and chronic (18 days) exposure to 4,300 m (HA). Mean $\dot{V}O_2$ max was ~ 27% lower with acute HA than at SL and did not change significantly with continued HA exposure. Biopsies from the vastus lateralis muscle and venous blood samples were obtained before and after 30 min of exercise, while determinations of the respiratory exchange ratio (R) were made at 10 min intervals during each of the submaximal bouts. Resting serum levels of free fatty

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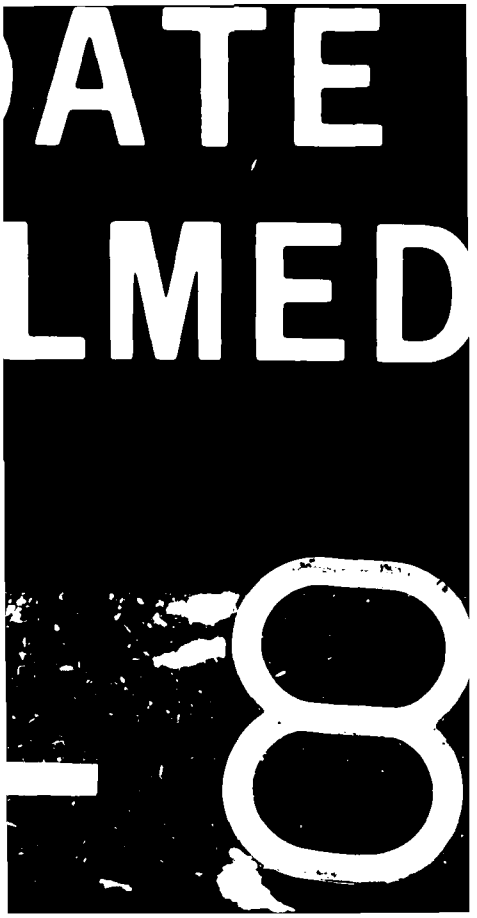
acids, unchanged with exercise, were 2X and 3X higher than SL with acute and chronic HA, respecitvely. Exercise did not alter resting serum glycerol levels at SL or during acute HA, but caused an 11-fold increase during chronic HA. Mean blood lactate concentrations were similar following exercise at SL and acute HA but were 87% lower after chronic HA. During exercise at SL and acute HA, the rate of muscle glycogen utilization and R were similar but were 41% and 15% lower, respectively, with chronic HA. These data suggest that after chronic high-altitude exposure, increased mobilization and use of free fatty acids during exercise resulted in sparing of muscle glycogen.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